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(54) Process for the manufacture of carotenoid compositions

(57) A method for the manufacture of carotenoid powders is disclosed. In the disclosed method, an aqueous suspension of the carotenoid is heated to melt the carotenoid, the suspension is then homogenized under pressure to form an emulsion, and the resulting emulsion is dried to obtain the carotenoid powder.

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Description

The present invention is r lated to a process for the manufacture of a substance powd r wherein the mean size of the substance particles in said powder is from 0.1 to 0.5 μm. Specifically, the present invention is related t a process for the manufacture of a solid carotenoid powder containing from 10 to 25% by weight of carotenoid particles wherein the mean size of said carotenoid particles in said powder is from 0.1 to 0.5 μm.

β-Carotene as well as other carotenoids such as e.g. lycopene, bixin, zeaxanthin, cryptoxanthin, lutein, canthaxanthin, astaxanthin, β-apo-8 'carotenal, β-apo-12'-carotenal as well as esters of hydroxy-and carboxy-containing compounds of this group, e.g., the lower alkyl esters, preferably the methyl ester and ethyl ester, have, acquired a considerable significance as colorants or color-imparting agents for foodstuffs or also as feed additives. More recently, it has been suggested that β-carotene is effective as a prophylactic against cancerous diseases.

However, carotenoids are substances which are insoluble in water, have high melting points and are also sensitive to heat and oxidation. These properties of carotenoids are especially disadvantageous in the coloring of aqueous media, since it is extremely difficult, because of their water-insolubility, to achieve a homogeneous or sufficiently intense coloring effect.

In the case of β-carotene (BC) these properties, especially the water-insolubility, give rise to extremely poor bioavailability from pharmaceutical dosage forms such as, for example, tablets, capsules etc. which contain this carotenoid. The aforementioned properties are, moreover, an obstacle to a direct use of crystalline β-carotene for the coloring of aqueous foodstuffs, as feed additives, or also for use as a source of vitamin A, since crystalline β-carotene is absorbed only poorly or imparts only a poor coloring effect.

Various processes for the manufacture of water-dispersible carotenoid compositions are already known from the literature, but these are all associated with certain disadvantages. Thus, for example, from German Patent No. 12 11 911 it is known to manufacture carotenoid compositions by dissolving a carotenoid, emulsifying the resulting solution into an aqueous solution of a protective colloid and subsequently removing the solvent from this emulsion. The disadvantage of this process resides in the fact that chlorinated hydrocarbons are preferably used as the solvent and their removal creates an environmental burden which makes the process extremely expensive from a commercial point of view. Furthermore, it is known from European Patent 65 193 to manufacture carotenoid compositions by dissolving a carotenoid in a non-chlorinated volatile water-miscible organic solvent at temperatures between 50° and 200°C within a period of less than 10 seconds, precipitating the carotenoid in colloid-dispersed form from the solution obtained by mixing with a solution of a colloid and subsequently removing the solvent. Here also an organic solvent must therefore be removed, which again is expensive on an industrial scale.

Alternatives to the use of organic solvents are well known. For example, the PCT application WO 91/06292 describes a process for milling of the carotenoid crystal in an aqueous medium. However, while the stability of the resultant powders are good, their tinctorial power in aqueous solutions and thus their bioavailability, are poor due to the coarse size of the carotenoid particle relative to that obtained with sub-micron emulsion techniques. Other methods, for example U.S. Patent 2,861,891, include the use of solubilizing oils to effect the desired particle size reduction. The use of the solubilizing oils is limited where, for example, there are concerns about the healthiness of the various oils, and where the manufacture of higher potency powders is desired, due to the limited solubility of the carotenoids, even when the oils are rendered supersaturated with carotenoid at elevated temperatures.

There accordingly exists a need for a process for the manufacture of higher potency powdered carotenoid compositions which is carried out without the use of organic solvents and/or solubilizing oils and which compositions are readily dispersible in aqueous media and which, moreover, in the case particularly of β-carotene, are suitable for the manufacture of pharmaceutical dosage forms having good stability and bioavailability of the active substance.

Specifically, the present invention comprises a novel process for the manufacture of colloid-dispersed carotenoid compositions and the thus manufactured compositions themselves. The compositions manufactured in accordance with the invention are useful, depending on the carotenoid which is used, not only for the manufacture of pharmaceutical dosage forms, but also for the coloring of foodstuffs and as feed additives.

By means of the process in accordance with the invention, it is now possible to avoid the aforementioned disadvantages and to obtain carotenoid compositions having the heretofore unattainable properties. We have discovered that carotenoid powders having a potency of up to 25% (potency being the percentage, by weight, of the carotenoid in the final composition) and having high tinctural power (and thus having the related high bioavailability) can be obtained by carrying out the present high temperature/high pressure (HTHP) process without the need for solubilizing oils or organic solvents. The resulting powders have excellent stability (shelf-life) and bioavailability in tablet applications.

The preferred process of the invention comprises melting the carotenoid, for example β-carotene, within an aqueous suspension of the carotenoid and a protective colloid by heating the suspension to 180°C to 250°C, preferably to 180°C to 225°C, more preferably to 185°C to 195°C, and homogenizing the suspension containing the melted carotenoid at a pressure of 96.6 to 2759 bar (1,400 to 40,000 psi), preferably 96.6 to 1034.5 bar (1,400 to 15,000 psi), more preferably 137.9 to 689.7 bar (2,000 to 10,000 psi), to obtain an emulsion, and drying the emulsion to obtain the carotenoid powder.

Figure 1 shows a schematic flow sheet for processing carotenoid crystals by th HTHP process in accordance with the invention whereby the reference signs mean:

1	stirring vessel
2 or M	mixer
3	high pressure pump
4	heat exchanger
5	homogenizing device
6	heat exchanger
7	collection vessel
8	stirring vessel
9	drying tower

The residence time of the carotenoid crystals in the heat exchanger was designed to be <60 seconds for melting of the carotenoid crystals.

Figure 2 shows a schematic flow sheet for processing carotenoid crystals by the HTHP process whereby the reference signs mean:

M	mixer
1	suspension vessel
2	crystal suspension mill
3	high pressure pump
4	primary heat exchanger
5	secondary heat exchanger
6	homogenizing device
7	Additional matrix vessel
8	pump
9	static in-line mixer
10	heat exchanger
11	valve
12	drying tower

The process was designed with a primary heat exchanger and a smaller secondary heat exchanger in series and having residence times of the carotenoid crystals in the heat exchangers of <30 and <3 seconds, respectively.

The present invention comprises a novel high temperature/high pressure (HTHP) process which is capable of producing high potency (up to 25% by weight) carotenoid powders (the powder particles themselves are referred to as "beadlets") having excellent tablet stability and bioavailability, without the need for carotenoid solubilizing oils or organic solvents, although their use is not precluded. The beadlets may comprise a matrix of a protective colloid, such as gelatin, with the carotenoid dispersed therein. Preferably, the matrix also comprises a plasticizer, such as a sugar. The process in accordance with the invention provides carotenoid beadlets in which the mean particle size of the carotenoid particles within the beadlet matrix are in the range from 0.1 to 0.5 microns, as measured by conventional laser light scattering instruments, such as a Malvern Zetasizer (Malvern Instruments Inc., Southborough, MA, U.S.A.).

The method of the invention comprises melting the carotenoid within an aqueous „feed" suspension containing the carotenoid, a surfactant and optionally a protective colloid by heating the suspension to 180°C to 250°C, preferably to 180°C to 225°C, more preferably to 185°C to 195°C, and homogenizing the suspension containing the melted carotenoid at a pressure of 96.6 to 2759 bar (1,400 to 40,000 psi), preferably 96.6 to 1034.5 bar (1,400 to 15,000 psi), more preferably 137.9 to 689.7 bar (2,000 to 10,000 psi), to obtain a carotenoid emulsion, and drying the emulsion to obtain the final composition, a carotenoid powder.

In accordance with the invention, it is preferred to cool the carotenoid emulsion immediately after homogenization by adding an aqueous "Addition Matrix." Such Addition Matrix contains a plasticizer, and may also contain additional protective colloid, antioxidants, microbial preservatives, and the like, for including in the final composition. The plasticizer in the Addition Matrix also acts to avoid the deleterious effects of high temperature, e.g., carmelization and the formation of Maillard products.

The preferred compounds for use with the process of the invention are the carotenoids. Examples of carotenoids are β-carotene, lycopene, bixin, zeaxanthin, cryptoxanthin, lutein, canthaxanthin, astaxanthin, β-apo-8'carotenal, β-apo-12'-carotenal, 2'-dehydroplectaniaxanthin, as well as esters of hydroxy-and carboxy-containing compounds of these compounds, e.g. the lower alkyl esters, preferably the methyl ester and ethyl ester. The especially preferred compound for use in the process of the invention is β-carotene. While the claimed process is described for processing carotenoids, especially β-carotene, one skilled in the art could apply the disclosed proc ss to other compounds having

similar physical and chemical properties with only routin changes in processing conditions. Examples of other compounds are drugs and the fat-soluble vitamins, especially vitamin A and its derivatives, and poly-unsaturated fatty acids and derivatives thereof.

Any conventional homogenizing device which is capable of operating under the temperature and pressure requirements of the present process may b used to practic the process of the invention. An example of such a conventional homogenizing device is a Rannie High Pressure Homogenizer (APV Corp., Wilmington, MA, U.S.A.).

The preferred homogenizing devices for practicing the process of the invention are those disclosed in U.S. Patents 4,533,254 and 4,908,154.

The especially preferred homogenizer is a device of the U.S. Patent 4,533,254 patent manufactured by Microfluidics Corp., Newton, MA, U.S.A., under the name Microfluidizer®. A recycling of the aqueous suspension in the homogenizing device as described in the aforementioned patents may be done to reduce the size of the dispersed carotenoid droplets and/or to make them of more uniform size.

The concentration of the careteniod in the aqueous feed suspension depends on the respective carotenoid which is used and on the intended use of the end product. Concentrations of carotenoid in the aqueous feed suspension which provide a potency in the range from 10% to 25% by weight of the final composition are preferred.

The carotenoid feed suspension also contains a surfactant. Any conventional surfactants, as is known to those skilled in the art, such as for example sorbitan derivatives, glycerol monostearate, citric acid esters and ascorbic acid 6-palmitate, etc. may be used in accordance with the invention. The amount of surfactant is typically 0.1 to 6.0% by weight based on the final composition and more preferably, 2 to 4% by weight. The preferred surfactant is ascorbyl palmitate (which also functions as an antioxidant) and is especially preferred when the carotenoid feed suspension has a pH of 6.5-7.5.

In addition to a carotenoid or a mixture of two or more carotenoids, and the surfactant, the aqueous feed suspension preferably contains a protective colloid in an amount from 5% to 75% by weight of the final composition. Any conventional protective colloids, as is known to those skilled in the art, such as gum acacia, gelatin, milk and vegetable proteins, starch and starch derivatives, etc., may be used in accordance with the invention. The preferred protective colloid is gelatin, from either fish or mammalian sources, having a bloom of 0 to 300.

All of the protective colloid need not be contained in the feed suspension. A portion may be added subsequent to the homogenization step as part of the Addition Matrix which is preferably added to the aqueous suspension to cool it immediately after homogenization. The amount of protective colloid in the feed suspension may range from about 10-30% by weight, preferably about 20% by weight, of total protective colloid in the final composition. The preferred ratio for the distribution of protective colloid between the feed suspension and the Addition Matrix is 1:1 to 1:9 and more preferably, 1:2 to 1:5.

Because carotenoids are subject to oxidation, the preparation of the carotenoid suspension is performed under an inert gas, e.g., nitrogen, and the suspension may also contain conventional antioxidants. The antioxidants preferred for β-Carotene are 1-8% by weight of sodium ascorbate, preferably 2-4% by weight, 0.1-6% by weight of ascorbyl palmitate, preferably 2-4% by weight, and 0.5-4% by weight of dl-alpha tocopherol, preferably 1-2% by weight, all based on a final composition having 10-25% by weight β-Carotene content. Antioxidants for other carotenoids and other compounds useful in the process of the invention are known to those skilled in the art. Examples are propyl gallate, butylated hydroxyanisole (BHT) and butylated hydroxytoluene (BHA). The suspension may also contain any conventional antimicrobial preservatives, such as the sorbates, parabens, benzoic acid, etc., in amounts that are conventionally used.

After the carotenoid in the feed suspension is melted and the feed suspension is homogenized, the resulting emulsion is preferably further processed by adding to the emulsion the Addition Matrix which contains the remaining protective colloid (if any) and a plasticizer so that the final composition desired may be achieved upon drying. Any conventional plasticizer, as is known to those skilled in the art, such as for example sugars, sugar alcohols, glycerin, etc., may be used in accordance with the invention. The preferred plasticizer is sucrose. When gelatin is the protective colloid, the ratio of gelatin to plasticizer in the final composition is in a range from 5:1 to 1:5 and preferably in the range from 2:1 to 1:2.

The completed carotenoid emulsion is converted into a dry, stable, powder form using any conventional means, as is known to those skilled in the art, such as spray drying, fluidized spray drying, or beadlet technology such as the oil suspension or starch catch methods known in the art. The preferred method of converting the emulsion to a dry powder is starch catch beadlet technology, such as that described in U.S. Patent 2,756,177.

The invention hereinafter shall be described with respect to the preferred compound for use with the invention, β-carotene (BC). This description is meant to exemplify, and not limit, the scope of the invention.

In accordance with the invention, the aqueous BC feed suspension is heated under pressure (with the pressure being at least sufficient to prevent boiling of the water) under conditions sufficient to melt the BC within about 1-60 seconds, preferably from 1-30 seconds, and then instantly homogenized in the homogenizing device. Preferably, the aqu - ous BC suspension is pressurized and then heated. Prior to processing the BC suspension and concurrent to the preparation of the BC suspension, the system is preferably first equilibrated on water to the required temperatur and

pressure. Flushes of dilute protective colloid solution may also be passed through th unit both prior t and immediat ly after the BC suspension, as a precautionary measure to prevent BC crystal formation and subsequent clogging f the device.

In order to minimize degradation and to control isomerization of the carotenoid so as to obtain the isomers most preferable for the intended biological effect, it is necessary to control the amount of time the carotenoid suspension is maintained at high temperatures ("residence time"). This is readily done in the design of the heat exchanger(s) by taking into consideration the size and volume of the heating surface, the suspension throughput, the temperature and pressure desired and the type of heat transfer media employed. Residence times of less than 60 seconds at temperatures above the melting point of BC are desirable, with residence times of less than 30 seconds at that temperature preferred. Most preferable are residence times of less than 30 seconds at temperatures which preclude isomeration but raise the suspension to temperatures that approach the melting point of BC, immediately followed by residence times of <3 seconds at temperatures at or above the melting point of BC. To further minimize the effects of high temperatures on the newly formed BC emulsion which exits the homogenizing device, it is desirable to add the Addition Matrix, i.e., protective colloid and/or plasticizers, having a temperature of 25-70°C to rapidly cool the hot emulsion, which is then further cooled in a heat exchanger to temperatures which are suitable for processing into a dry powder.

Additionally, to minimize the exposure time of BC to the potential effects of high temperatures, it is advantageous to use BC where 90% of the particles, as measured by laser light scattering (D[V,0.9]), are less than 30 microns. Preferably, it is desired to use BC having a particle size of less than 3 microns (D[V,0.9]), as measured by laser light scattering. When BC crystals of a particle size less than 3 microns are not available, it is preferred to obtain such by milling larger BC crystals to that smaller size. This is readily accomplished by passing the aqueous suspension of BC through, for example, a ball mill, repeatedly, if necessary, until the desired particle size is obtained.

The entire process can be carried out either in a continuous or batchwise mode. The process in accordance with the invention can be carried out, for example in apparatus as are shown in Figure 1 and Figure 2.

Figure 1 shows an apparatus for carrying out the present invention. In a suitable size stainless steel vessel (1), carotenoid crystals (90% of the particles having a size of less than 30 microns) are first suspended by high shear mixing (2) in an aqueous solution of a surfactant, which may also contain protective colloid, microbial preservatives and antioxidants. This carotenoid feed suspension is then pressurized via a pneumatically powered pump (3) and processed, first through a helical coil type heat exchanger (4), whose temperature is controlled by circulating hot oil to the shell side of the unit, to melt the crystals in a short time (<60 seconds), and then through an interaction chamber (5) where homogenization occurs instantaneously, resulting in a sub-micron carotenoid emulsion. The emulsion is then cooled (60°-85°C) by passage through a second heat exchanger (6) and collected in a suitable container (7). The resulting emulsion is further processed by mixing with the Addition Matrix containing the remaining protective colloid (if any), a plasticizer and any antioxidants to achieve the desired formula which will have the desired composition and potency upon drying. The "Addition Matrix" is prepared in parallel in a suitable size vessel equipped with a high shear mixer (8). The completed emulsion is then converted into a dry, stable, final carotenoid powder form using conventional starch catch beadlet technology (9).

Figure 2 shows a further embodiment of the process scheme for carrying out the present invention. The aqueous feed suspension of a carotenoid is prepared under an inert atmosphere in a suitable size jacketed stainless steel vessel equipped with an agitator (1). The suspension contains a surfactant, and optionally protective colloid, microbial preservatives and antioxidants. The suspension is milled in a ball mill (2) until 90% of the carotenoid particles have a size of less than 3 microns. The milled suspension is then metered with a high pressure pump (3) into the first heat exchanger (4) where the temperature of the suspension approaches the melting point of the particular carotenoid, then into the second heat exchanger (5) wherein the carotenoid is completely melted. The residence time in these two helical coil type heat exchangers is <30 and <3 seconds, respectively. The temperatures of the heat exchangers are controlled by regulating the steam pressure on the shell side of the units. The solution then passes through a high pressure homogenizing device (6) where a submicron emulsion of the carotenoid is produced. In parallel to these events, the aqueous "Addition Matrix," which may contain protective colloids, plasticizers, antioxidants and microbial preservatives, is prepared in a suitable size jacketed stainless steel vessel equipped with an agitator (7) and then metered with a pump (8) at such a rate as to achieve the desired formula composition and potency. The streams from the Addition Matrix and the carotenoid emulsion are then combined in a static mixer (9) where they become homogeneous prior to being cooled in a heat exchanger (10). The emulsion pressure is then reduced to atmospheric as it passes through a pressure control valve (11) and the completed emulsion is then converted into a dry, stable, final carotenoid powder form by using conventional starch catch beadlet technology (12).

Example 1

Preparation of a 20% β-Carotene Powder

A. Preparation of a β-Carotene Feed Suspension

First water, then the following ingredients were added to a suitable size stainless steel pot and mixed and then the pot was placed in a water bath (ca 70°-80°C) for 1-2 hours to hydrate the gelatin.

	g
Gelatin (140 bloom)	286.4
Sodium Benzoate	20
Sorbic Acid	7.5
Methyl Paraben	3.25
Propyl Paraben	0.38
Sodium Ascorbate	5
Distilled Water	1755

50 g ascorbyl palmitate were added in portions to the gelatin solution while mixing with a suitable high shear mixer (e.g., Gifford-Wood) to ensure uniform distribution. The mixture was adjusted to pH 7.2-7.8 with 20% w/w sodium hydroxide solution. While mixing with the high shear mixer, 50 g dl-alpha tocopherol and 575 g β-carotene crystals were slowly added to the mixture. The particle size of the BC crystals, as determined by a Malvern Mastersizer X Particle Size Analyzer, was 90% less than 30 microns. The pH was controlled and re-adjusted to 7.2-7.8 (if necessary). The β-carotene suspension was hold in a water bath (70-80°C) until to process further and re-mixed just prior to further processing so as to ensure homogeneity.

B. Preparation of a β-Carotene Emulsion

The system was quilibrated (Fig 1) with distilled water to obtain the desired pressure and temperature. The temperature of the circulating fluid in the oil heating unit was first adjusted to ensure that the process is operated at the target conditions. A Microfluidizer® Model M110ET was used as the homogenizing device.

Feed Suspension Inlet Temp:	210°-215°C
Emulsion Outlet Temp:	60°C
Pressure:	413.8 bar (6000 psi)

When equilibrated, feeding the BC suspension to the intake of the pump began and the β-carotene emulsion was collected in a suitable container.

C. Preparation and Addition of Addition Matrix to Emulsion

Only a portion, 2000 g, of the β-carotene emulsion produced in step B was used for further processing. In a manner similar to step A, the Addition Matrix was prepared and then added to the BC emulsion, mixed and then (if necessary) the pH adjusted to 6.8-7.2 with 20% sodium hydroxide solution.

Addition Matrix	g
47% w/w Gelatin Solution	401.6
Sucrose	374.7
Sodium Ascorbat	66.6
Distilled Wat r	108

D. Preparation of Powder

The completed emulsion was then converted into a dry powder by spraying into a bed of chilled starch, subsequently separated by sieving and the resulting powder, then dried to a moisture content of 5-6% in a fluid bed dryer.

Example 2

A. The powder produced in Example 1 has the following mesh profile as determined by sieve analysis (U.S. Standard).

Wt % on 40 mesh	0.1
50 mesh	3.5
60 mesh	17.5
80 mesh	77.1
100 mesh	0.8
Pan	1.0

B. A sample of this powder was re-dispersed with moderate agitation in warm distilled water, and found to impart significant color to the solution. An indication of this good tinctorial power is the determination of the E^1_1 value* which was found to be 1147.

Example 3

Stability results for the powder, per se, and in two different tablet applications are shown below:

		Per Se	Multivitamin + Iron*	Multivitamin + Minerals*
Initial BC Assay:		19.3%	4.1 mg/tablet	0.8 mg/tablet
			% BC Retention (Based on initial assay)	
Storage Conditions:		Rentension (%)**	Rentension (%)**	Rentension (%)**
45°	1 month	98		
	3 months	95		
	6 months	97		
RT	1 month	96	98	121
	3 months	98	95	118
	6 months	98	95	119
	9 months	99	100	101

*Formulation and tablet procedures are as described in Examples 7 and 8.
**Analysis by HPLC

Example 4

β-Carot ne powders of different compositions wer prepared accordingto the following in a manner analogous to Example 1 (Expt. = Experiment).

* Procedure as shown in Example 8, which is a standard measure of absorptivity

	Expt. 1	Expt. 2	Expt. 3	Expt. 4
Ratio Gelatin in Feed Susp nsion to Addition Matrix	1:1	1:1	1:4.2	1:0
Ratio Gelatin to Sucrose in Final Powder	1:1	1:2	1:1	1:1
BC Suspension:	Grams			
Gelatin (140 Bloom)	286.4	403.0	173.2	915.9
Sodium Benzoate	20.0	32.0	24.0	24.0
Sorbic Acid	7.5	12.4	9.3	9.3
Methyl Paraben	3.25	5.2	3.9	3.9
Propyl Paraben	0.38	0.56	0.42	0.42
Sodium Ascorbate	5.0	--	--	--
Distilled Water	1755	2342	1546	2855
Ascorbyl Palmitate	50.0	52.0	39.0	39.0
20% w/w NaOH Solution	adjusted pH: 7.2 to 7.8			
dl-Alpha Tocopherol	50.0	72.0	54.0	54.0
BC Crystals	575.0	720.0	543.9	543.9
Addition Matrix:				
Gelatin Solution (47% w/w)	401.6	550.2	791.6	--
Sucrose	374.7	1023.4	459.8	592.3
Sodium Ascorbate	66.6	--	--	--
Distilled Water	108.	595	--	--
20% w/w NaOH Solution	adjusted pH: 6.8-7.2 (if necessary)			
Weight Emulsion Mixed with Additional Matrix:	2000	2423	1300	3100
Process Conditions:				
Pressure (bar) ((psi))	413.8 (6000)	689.7 (10,000)	689.7 (10,000)	172.4 (2500)
Inlet Temperature (°C)	213-227	222	213-215	195-197
Flow Rate (γ/min)	578	740	670	320
Outlet Temperature (°C)	62-68	78	80	71-72
Powder Characteristics:				
Particle Size, Internal Phase, Mean Diameter	235 nm	190 nm	272 nm	259 nm
BC Content (HPLC Assay)	19.3%	18.4%	16.4%	16.4%
-Trans BC Content	45%	33%	36%	35%

Example 5

Lycopene powders were prepared and in a manner analogous to Example 1. Compositions had a gelatin to sucrose ratio of 1:1 and were formulated with and without oil (peanut).

	Expt. 5	Expt. 6
Ratio Gelatin in Feed Suspension to Addition Matrix:	1:1	1:3.1
Lycopene Suspension:	Grams	
Fish Gelatin	95.9	67.5
Distilled Water	571.5	1343
Ascorbyl Palmitate	20.0	30.0
20% w/w NaOH Solution	adjusted pH: 7.2 to 7.5	
dl-Alpha Tocopherol	15.0	22.5
Peanut Oil	--	45.0
Lycopene Crystals	120.0	180.0
Addition Matrix:		
Fish Gelatin	54.7	47.0
Sucrose	195.5	107
Distilled Water	44.4	--
Weight Emulsion Mixed with Additional Matrix:	468.7	382
Process Conditions:		
Pressure (bar) ((psi))	413.8 (6000)	206.9 (3,000)
Inlet Temperature (°C)	209-217	206
Flow Rate (g/min)	387	268
Outlet Temperature (°C)	40-42	47
Powder Characteristics:		
Particle Size, Internal Phase Mean Diameter	221 nm	320 nm
Lycopene Content (UV)	8.9%	7.8%
-Trans Lycopene Content	46%	45%
Color Intensity (E|)	851	657

Example 6

The following carotenoid powders were prepared in a manner analogous to Example 1 but with larger batch sizes so as to provide continuous run times of 2 1/2 to 3 hours. For these trials, the process scheme is illustrated by Fig 2.

	Expt. 7	Expt. 8	Expt. 9
	20% BC Powder	10% BC Powder	5% 2'DHP Powder
CAROTENOID FEED SUSPENSION:	Kg/100 Kg		
β-Carotene	22.97	9.42	--
2'Dehydroplectaniaxanthin	--	--	10.4
dl-Alpha Tocopherol	1.6	0.68	1.73
Ascorbyl Palmitate	3.74	1.78	1.73
Na Ascorbate	0.24	--	--
Gelatin (140 Bloom)	6.07	22.0	13.79
Sodium Hydroxide (28% w/w Sol)	0.38	1.57	0.34
Water	65.0	64.55	72.0
ADDITION MATRIX:	Kg/100 Kg		
Gelatin (140 Bloom)	21.7	--	22.18
Sucrose	24.57	40	11.22
Yellow Dextrin	--	--	11.22
Sodium Ascorbate	2.35	--	--
Sodium Hydroxide (28% w/w Sol)	0.15	--	0.21
Water	51.24	60	55.18

Operating Conditions:

High Pressure Homogenizing Device	Microfluidic s IX*-Chamber	Rannie HP Valve (12.51 H)	Microfluidic s IX*-Chamber
Gelatin Distribution Between Suspension and Addition Matrix	1:3.7	1:0	1:4
Particle Size Carotenoid (D[V,0.9]) µm in Suspension	2.3	20	3.1
Temperature Suspension(°C)	60	60	60
Temperature Matrix(°C)	60	60	60
Temperature Addition Matrix(°C)	50	RT	50
Solid Content of Suspension (%)	35	34	28
Solid Content of Emulsion(%)	42	36	40
Feed Rate Suspension/Matrix(kg/h)	38	50	38
Feed Rate Addition Matrix(kg/h)	39.3	27.5	94.7
Pressure after HE* 1(bar)	190-200	460	170-190
Pressure after HE 2(bar)	190-200	460	172-180
Temperature after HE** 1(°C)	160	130-140	160
Temperature middle of HE 2(°C)	195	215	190
Pressure after Homogenizing Device(bar)	27	27	27
Temperature after the Static Mixers(°C)	121	135	92
Temperature at the Emulsion Outlet(°C)	60	60	67-68

* IX = Interaction

** HE = Heat exchanger

Powder Characteristics:

Particle Size, Internal Phase, Mean Diameter		261 nm	212 nm	362 nm
Assay:	BC (HPLC)	21.4%	11.2%	--
	2'-DHP (UV)	--	--	5.6%
	% Trans	52	46	61
Color Intensity E_1^1		944	1235	845

Example 7

Preparation of multivitamin-multimineral tablets

FORMULATION	
Ingredients	mg/Tablet
1. β-carotene 20% Beadlets	4.50*
2. Dry Vitamin E Acetate 50% SD	63.00
3. Ascorbic Acid 90% Granulation	105.00
4. Folic Acid	0.50
5. Thiamine Mononitrate	2.48
6. Riboflavin Type S	2.86
7. Niacinamide Free Flowing	21.00
8. Pyridoxine Hydrochloride	4.00
9. Vitamin B12 0.1% SD	11.70
10. BITRIT-1®**	5.63
11. Calcium Pantothenate	14.67
12. Ferrous Fumarate (32.87% Fe)	82.20
13. Cupric Oxide (79.88% Cu)	3.76
14. Zinc Sulfate Dried (36.43% Zn)	61.76
15. Manganese Sulfate Monohydrate (32,5% Mn)	23.10
16. Potassium Iodide Stabilized (68% I_2)	0.22
17. Potassium Chloride (52.4% K) (47/6% Cl)	14.70
18. Magnesium Oxide USP/DC E.M. (60% Mg)	166.67
19. Dicalcium Phosphate Dihydrate, Unmilled (23.3% Ca) (18.0% P)	696.00
20. Modified Food Starch (Explo-Tab)	70.00
21. Modified Cellulose Gum (Ac-Di-Sol)	47.00
22. Microcrystalline Cellulose (Avicel PH102)	50.75
23. Stearic Acid	4.00
24. Magnesium Stearate	8.00
TOTAL TABLET WEIGHT (mg)	1463.50

* β-carotene input was based on actual assay.
** trademark of F. Hoffmann-La Roche Ltd.; 1% delution of biotin in calcium phosphate

Tablet manufacturing procedure

1. Mix items 4-11. Mill through a hammer mill having a No. 0 plate, hammers at medium speed. Remix and set aside as part A.

2. Mix items 1, 2, and 3. Set aside as part B.

3. Mix items 12-17. Set hammer mill to use knives. Mill through a No. 0 plate on a Fitzpatrick mill, knives at medium speed. Remix and set aside as part C.

4. Mix parts A, B, and C with items 18, 20, 21, and 22 for 10 minutes. Add and mix item 19. Mix for 10 minutes.

5. Add items 23 and 24 as a premix with a screened (through 30 mesh) portion of the blend. Mix for 2 minutes.

6. Compress at 3 tons on Stokes Single Punch Instrumented Tablet Press with 0.78 x 1.88 cm (5/16" x 3/4") capsule-shaped punches.

7. Mix 23 and 24. Screen through 30 mesh and mix with the material from step 4 for two minutes.

According to the above procedure tablets were prepared.

Example 8

Preparation of multivitamin tablets with iron

FORMULATION	
Ingredients	mg/tablet
1. Acetabeads Type 500A	2.70
2. Acetabeads Type 500A/50D3	10.80
3. β-Carotene 20% Beadlets	20.25*
4. Dry Vitamin E Acetate 50% SD	66.00
5. Ascorbic Acid 90% Granulation	80.00
6. Folic Acid	0.50
7. Thiamine Mononitrate	1.73
8. Riboflavin Type S	1.87
9. Niacinamide Free Flowing	22.00
10. Pyridoxine Hydrochloride	2.67
11. Vitamin B12 0.1% SD	7.50
12. BITRIT-1®	16.50
13. Calcium Pantothenate	14.00
14. Ferrous Fumarate (32.87% Fe)	54.70
15. Corn Starch (Sta-Rx 1500)	20.00
16. Microcrystalline Cellulose (Avicel PH102)	60.00
17. Dicalcium Phosphate Dihydrate, unmilled	37.03
18. Magnesium Stearate	2.00
TOTAL TABLET WEIGHT (mg)	420.25

* β-carotene input was based on actual assay.

Tablet manufacturing procedure

1. Blend items 6, 7, 8, 10, 11, and 12 for 5 minutes. Add items 9 and 15. Mix for 10 minutes. Mill through a No. 1A plate on a Fitzpatrick mill, medium speed with knives forward.

2. Add items 1, 2, 3, and 13 as a premix with a portion of the blend. Mix for 10 minutes.

3. Add items 4, 5, 14, 16, and 17. Mix for 10 minutes.

4. Screen a portion of mixture from step 3 through a 30 mesh screen and mix with item 18. Mix this combination with the remainder of the step 3 mixture for 2 minutes.

5. Compress at 2 tons on Stokes Single Punch Instrumented Tablet Press using a deep concave punch (diameter 0.94 cm (3/8")) at rate of 52 tablets/min.

According to the abov procedure tablets were prepared.

Example 9

Procedure for the Estimation of the Tinctorial Power

Ca. 100 mg powder (or emulsion) is accurately weighed into a 100 ml volumetric flask and dissolved in ca. 50 ml of distilled water at 50°C and sonicated for 5 minutes. Subsequently, the emulsion is cooled and filled to the mark with distilled water. 5 ml of this solution is diluted with distilled water to give 100 ml (= test solution). This test solution is analyzed in the spectrophotometer against a water blank at 200 nm to 650 nm. The photometer analysis was and should be performed as rapidly as possible after the preparation of the solutions. The analysis was performed in amber glassware. The analysis was performed in amber glassware. If the analysis is not performed in amber glassware, the work should be performed away from bright lights.

The maximum absorptivity (E) occurring at a wavelength (λ max) between 450-500 nm and corrected for the absorptivity at 650 nm was used to calculate the E^1_1 in water which is taken as a measure of the tintorial power or color intensity. This is calculated, as follows:

$$E^{1\%}_{1cm} = \frac{E_{max\lambda} \times 1000 \times 100 \times 100}{\text{Sample wt. (mg)} \times 5 \times \beta\text{ - carotene content}}$$

Claims

1. A process for the manufacture of a substance powder wherein the mean size of the substance particles in said powder is from 0.1 μm to 0.5 μm, comprising:

   a) melting an aqueous suspension containing the substance and 0.1-6% by weight of the final powder of a surfactant by heating the suspension, if required, at a temperature sufficient to melt said substance;

   b) homogenizing the melted aqueous substance suspension at a pressure in the range of 1,400 to 40,000 psi to obtain said particles of the substance;

   c) drying the homogenized, melted aqueous substance suspension to obtain said solid substance powder.

2. The process of claim 1 wherein the substance powder contains from 10 to 25% by weight of the substance particles and wherein in step a) the suspension contains 10 to 25% by weight of the final substance powder of the substance.

3. The process of claim 1 or 2 wherein said aqueous suspension further comprises 5 to 75% by weight of the final substance powder of a protective colloid.

4. The process of any one of the claims 1-3 wherein the substance is at least one of the group consisting of a carotinoid, a drug, a fat-soluble vitamin or a poly-unsaturated fatty acid and derivatives thereof.

5. A process for the manufacture of a solid carotenoid powder containing from 10 to 25% by weight of carotenoid particles wherein the mean size of said carotenoid particles in said powder is from 0.1 to 0.5 μm, comprising:

   a) melting an aqueous suspension containing 10 to 25% by weight of the final powder of carotenoid crystals and 0.1 to 6% by weight of the final powder of a surfactant by heating the suspension, at a temperature sufficient to melt said carotenoid crystals;

   b) homogenizing the melted aqueous carotenoid suspension at a pressure in the range of 96.6 to 2759 bar (1,400 to 40,000 psi) to obtain said particles of β-carotene;

   c) drying the homogenized, melted aqueous carotenoid suspension to obtain said solid carotenoid powder.

6. The process of claim 5 wherein said pressure is in the range from 96.6 to 1034.5 bar (1,400 to 15,000 psi).

7. The process of claim 5 or 6 wherein said aqueous carotenoid suspension further comprises 5 to 75% by weight of the final powder of a protective colloid.

8. The process of any one of the claims 5 to 7 wherein said carotenoid is β-carotene.

9. The proc ss of any one of the claims 5 to 8 wherein said temperature is in the range from 180°C to 250°C.

10. The process of claim 9 wherein said temperature is in the rang from 180°C to 225°C.

11. The process of claim 10 wherein said temperature is in the range from 185°C to 195°C.

12. The process of claim 11 wherein said pressure is in the range from 137.9 to 689.7 bar (2000 to 10,000 psi).

Figure 1

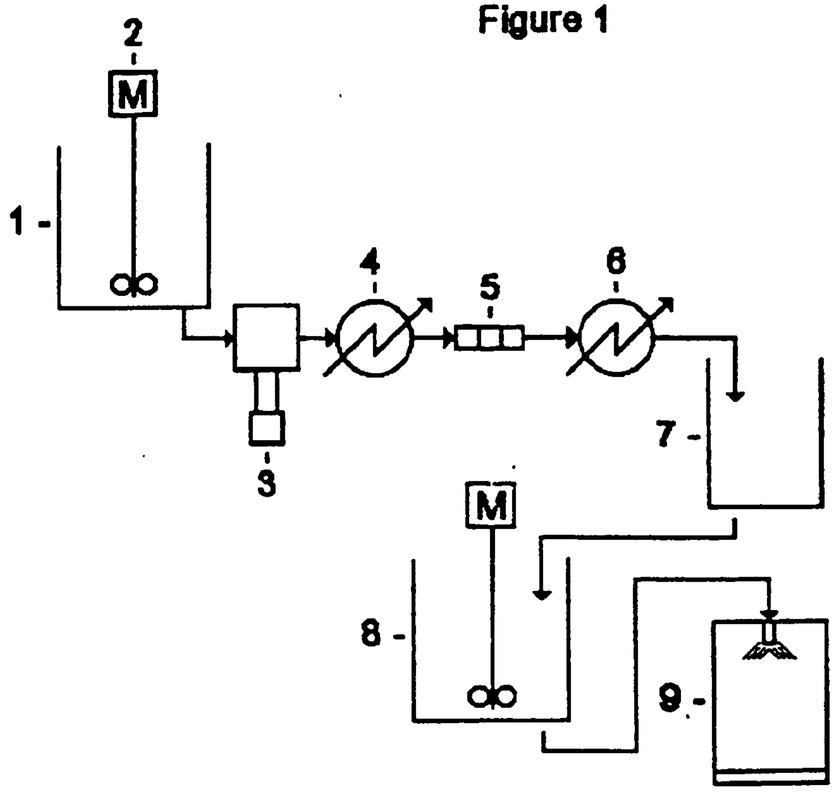

Figure 2